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## HEMORRHAGIC COLITIS ASSOCIATED WITH A RARE *ESCHERICHIA COLI* SEROTYPE

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**Abstract** We investigated two outbreaks of an unusual gastrointestinal illness that affected at least 47 people in Oregon and Michigan in February through March and May through June 1982. The illness was characterized by severe crampy abdominal pain, initially watery diarrhea followed by grossly bloody diarrhea, and little or no fever.

It was associated with eating at restaurants belonging to the same fast-food restaurant chain in Oregon ( $P < 0.005$ ) and Michigan ( $P = 0.0005$ ) and with eating any of three sandwiches containing three ingredients in common (beef patty, rehydrated onions, and pickles).

**I**N the first half of 1982 two outbreaks of an unusual gastrointestinal illness characterized by sudden onset of severe abdominal cramps and grossly bloody diarrhea, with no fever or low-grade fever, occurred in Oregon and Michigan. Isolated cases of a similar illness had recently been reported from Japan<sup>1</sup> and the United States,<sup>2-5</sup> but the etiologic agent had not been identified. The outbreaks in Oregon and Michigan led

to intensive epidemiologic and laboratory investigations. In this report we describe the illness and the evidence that it is associated with a rare serotype of *Escherichia coli* that is neither invasive nor enterotoxigenic according to standard tests and is not a recognized enteropathogenic *E. coli*.

## METHODS

### Epidemiologic Investigation

We defined as a case an illness characterized by severe abdominal cramps, grossly bloody diarrhea, and stool examinations that did not yield shigella, salmonella, campylobacter, ova, or parasites.

To find cases, we contacted local physicians, reviewed records of chief complaints in emergency rooms and discharge records from December 1981 to February 1982 in parts of Oregon, and from May to June 1982 in parts of Michigan, and began active surveillance in all hospitals in the affected areas and nearby counties. In both states

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we conducted case-control studies with either one or two age-matched and neighborhood-matched controls for each case, using a questionnaire developed after intensive interviews of reported cases. We examined specific food exposures at restaurants implicated by the Michigan neighborhood case-control study, by comparing foods eaten by cases and by controls selected from persons who had visited the restaurants with the cases and had remained well. Food-handling procedures, food delivery and turnover, and employee records were reviewed at the implicated restaurants. In Michigan, grill temperature was measured in one implicated restaurant by means of a rapid readout surface pyrometer (Pyrcon, type 4000A, Alnor Instruments). Logistic regression analysis, the binomial test, and the Pike-Morrow extension of the Mantel-Haenszel test were used for statistical analyses.<sup>6</sup>

### Laboratory Investigation

Stool specimens from cases were examined at the local hospital and state health-department laboratories for salmonella, shigella, campylobacter, ova, and parasites in both states and for *Yersinia enterocolitica* in Oregon. Stool specimens from some cases and controls were frozen ( $-70^{\circ}\text{C}$ ) until examination at the Centers for Disease Control (CDC). In Oregon, stool specimens were also collected from 45 persons who visited emergency rooms because of nonbloody diarrhea. Environmental samples, including food, were collected at implicated food establishments.

At the CDC, stool specimens from the outbreaks were examined for salmonella, shigella, pathogenic vibrios, *Y. enterocolitica*, campylobacter species, bacillus species, *Staphylococcus aureus*, enterotoxigenic and enteroinvasive *E. coli*, and anaerobes (including *Clostridium difficile* and toxin).<sup>7</sup> Five *E. coli* isolates from each stool were serotyped. The stool specimens were also examined for viruses by electron microscopy, by immunoelectron microscopy with acute-phase and convalescent-phase serum, and by culture in rhesus-monkey and human-fibroblast tissue cells.<sup>8,9</sup> The 45 diarrheal stool specimens obtained at emergency rooms were examined for *E. coli* 0157 and klebsiella. The foods were examined for *E. coli* 0157 and *Bacillus pumilus*.

*E. coli* 0157:H7, *Klebsiella oxytoca*, and *B. pumilus* isolates were tested for invasiveness by the Sereny test, for heat-stable toxin production by the suckling-mouse assay, and for heat-labile toxin production by the Y-1 adrenal-cell test.<sup>10</sup> *E. coli* 0157:H7 was tested in an infant-rabbit assay (Potter ME: personal communication).

The *E. coli* serotyping records of the U.S. Department of Agriculture Animal Laboratories at Ames, Iowa, the Pennsylvania State University Veterinary Science Laboratory, and the CDC Enteric Reference Laboratory were reviewed for previous identifications of *E. coli* 0157:H7.

### CASE REPORT

The following case report is typical of the cases seen in both outbreaks. A 56-year-old man was awakened by severe abdominal cramps in the right lower quadrant. Later the same morning, watery diarrhea developed, with bowel movements every 15 to 30 minutes. The patient initially noted small amounts of blood, but later the same day the diarrhea became grossly bloody, with bright-red blood, described as "all blood and no stool." He had slight nausea but no vomiting. He was hospitalized on the following day with continuous crampy abdominal pain and frequent bloody diarrhea. He was afebrile and on abdominal examination had no guarding, rebound tenderness, or distension. The white-cell count was 17,900 with a slight shift to the left. A barium enema revealed edema of the ascending and transverse colon, with areas of spasm. Examinations of three stool specimens collected within three days after the onset of illness did not detect salmonella, shigella, campylobacter, yersinia,

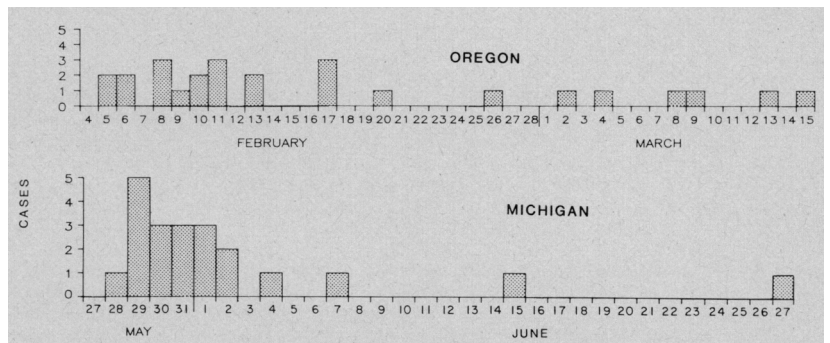


Figure 1. Cases of Hemorrhagic Colitis, According to Date of Onset (1982).

ova, or parasites. The patient was treated with intravenous fluids and doxycycline, and the bloody diarrhea subsided by the fifth hospital day. He was discharged the next morning.

## RESULTS

### Clinical and Epidemiologic Investigations

In Oregon, 25 persons from seven municipalities in one county and one person from an adjacent county became ill between February 5 and March 15 (Fig. 1). The median age was 28 years, with a range of 8 to 76 years; there were 16 males and 10 females. All consulted a physician, and 19 (73 per cent) were hospitalized. The duration of illness ranged from two to nine days, with a median of four days. In Michigan, 21 persons had onset of illness between May 28 and June 27 (Fig. 1). The median age was 17 years, with a range of 4 to 58 years. All consulted a physician, and 14 (67 per cent) were hospitalized. The illness lasted from three to more than seven days.

The symptoms in both outbreaks are shown in Table 1. Three patients in both outbreaks had temperatures of  $38.5^{\circ}\text{C}$  or more. The white-cell count ranged from 7600 to 19,600 (mean, 14,000) in Oregon and from 7600 to 17,400 (mean, 13,000) in Michigan, with a slight to moderate shift to the left. The erythrocyte sedimentation rates, serum electrolyte concentrations, liver-function tests, prothrombin times, and urinalyses were normal in all patients in whom these tests were done. Sigmoidoscopy performed in 10 patients revealed moderately hyperemic mucosa in 3. In six of seven patients barium enemas demonstrated marked submucosal edema with spasm and a "thumb-printing" pattern in the ascending and transverse colon (Fig. 2). In Oregon, 11 of 23 patients whose treatment histories were available received tetracycline compounds (eight patients) or erythromycin (three patients). The mean duration of illness of the group treated with antimicrobials was not significantly different from that of the untreated group. No transfusions were administered. There were no deaths, complications, or sequelae in any of the cases.

In Oregon, 25 of 26 cases and 47 neighborhood controls were interviewed. During the two weeks before onset of illness, 21 of 25 cases (84 per cent) but only 13 of 47 controls (28 per cent) had eaten at Restaurant 1,

one of a chain of fast-food restaurants (Chain A) ( $P < 0.005$  by logistic regression analysis). Three of the four who did not recall having eaten at Restaurant 1 had eaten at another Chain A restaurant within a week before the onset of illness.

The patients who ate at one of the three restaurants of Chain A in the county were more likely (21 of 24) to have eaten one of the chain's specialty hamburgers than were neighborhood controls (11 of 20) who had eaten at the same restaurants ( $P < 0.05$ , logistic regression analysis). The three patients who did not eat a specialty hamburger ate a regular hamburger (one patient) or a cheeseburger (two patients). The three types of sandwiches shared three ingredients, which were always served together — i.e., reconstituted dehydrated onions, standard-size hamburger meat patties, and pickles. Each of these three ingredients was eaten by a higher proportion of cases than of neighborhood controls ( $P < 0.05$ , Pike–Morrow extension of the Mantel–Haenszel test), but no single ingredient could be independently associated with disease, because they had always been served together.

In Michigan, 18 of 21 cases and their age-matched neighborhood controls were interviewed. (Matched controls could not be found for two cases.) Seventeen of 18 cases and 4 of 16 controls had eaten at either Restaurant 2 or Restaurant 3 of Chain A within 10 days before the onset of illness ( $P = 0.0005$ , binomial test). No other exposures were significantly associated with illness. Again, cases were more likely than their restaurant controls to have eaten the same three food items implicated in Oregon (17 of 17 vs. 12 of 19;  $P < 0.05$ , Pike–Morrow extension of the Mantel–Haenszel test). The mean period between single exposures to the implicated foods and onset of crampy abdominal pain was 3.9 days in Oregon and 3.8 days in Michigan. The attack rate for persons eating sandwiches that included the three ingredients was estimated to be about 1 case per 1000 sandwiches in Oregon, and 1.8 cases per 1000 for specialty hamburgers in Michigan, and 0.6 case per 1000 regular hamburgers and cheeseburgers in Michigan. The specialty ham-



Figure 2. Barium-Enema Radiograph in a Case of Hemorrhagic Colitis.

The area of "thumbprinting" (arrow) in the transverse colon suggests submucosal edema, a characteristic finding in this disease.

burger had twice the quantity of meat (two patties vs. one) and onions as the regular hamburger or cheeseburger.

Only one case of bloody diarrhea occurred among employees at the three restaurants. None of the family members of the cases in Oregon and Michigan had bloody diarrhea. In Michigan, 4 of 13 persons who had accompanied the cases to the implicated restaurants and had eaten one of the implicated foods had cramps and diarrhea without blood in one to seven days, whereas none of 12 who had not eaten these foods were ill ( $P = 0.06$ , Fisher's exact test, one-tailed).

There were no obvious defects in equipment or food-handling practices in the Oregon or Michigan restaurants. In Michigan, inadequate stock rotation of some foods was observed in Restaurant 2, and during busy periods certain parts of the grill were cooler than the temperature standard established by Chain A.

**Laboratory Investigation**

*E. coli* 0157:H7, *B. pumilus*, and *K. oxytoca* were the only bacteria isolated from three or more cases in either outbreak. *E. coli* 0157:H7 was recovered from stool of three of six Oregon cases and none of 10 neighborhood controls ( $P = 0.03$ , Fisher's exact test, one-

Table 1. Distribution of Symptoms in 43 Cases of Hemorrhagic Colitis.

SYMPTOM	OREGON (N = 25)	MICHIGAN (N = 18)	COMBINED (N = 43)
	<i>per cent with symptoms*</i>		
Bloody diarrhea †	100	100	100
Abdominal cramps †	100	100	100
Nausea	60	67	63
Vomiting	44	61	49
Chills	28	33	30
URI symptoms ‡	12	28	19
Fever (>38°C)	8	6	7

\*Based on all cases with complete clinical history.

†Part of case definition.

‡Upper-respiratory-tract infection.

tailed). An additional patient with *E. coli* 0157:H7 was identified by screening *E. coli* isolates sent to the CDC from Oregon. *K. oxytoca* was isolated from two cases and no controls (it was isolated in Oregon from one of the controls); *B. pumilus* was isolated from two cases and one control. *Y. enterocolitica* was recovered from one case only on cold enrichment, suggesting small numbers of organisms. Examination of the 45 control emergency-room diarrheal stool specimens yielded *K. oxytoca* from two samples and *E. coli* 0157:H7 from none. In the virologic studies we did not detect viral particles on electron microscopy or immunoelectron microscopy or in tissue cultures.

*E. coli* 0157:H7 was recovered from 6 of 14 specimens from cases and none of 4 specimens from controls in Michigan. *K. oxytoca* and *B. pumilus* were each isolated from three cases. In both states combined, *E. coli* 0157:H7 was isolated from 9 of 12 stools collected within four days after the onset of illness, but from none of 7 stools collected seven or more days after onset ( $P = 0.002$ , Fisher's exact test, one-tailed). In both outbreaks 0157:H7 was the predominant *E. coli* isolated (median of four of five isolates serotyped). The serotypes of *K. oxytoca* from patients' stools were different. The *E. coli* and *K. oxytoca* were sensitive to all antimicrobial agents tested, and the *B. pumilus* had two different antimicrobial-susceptibility patterns.

*E. coli* 0157:H7 was not isolated from food samples collected in Oregon but was isolated from a frozen, raw, standard-size hamburger patty from a suspected lot used at the Michigan restaurants during the outbreak period. This patty had been stored at a processing plant in another state, as part of a quality-control program, and had never been in either restaurant.

*E. coli* 0157:H7 did not produce either heat-labile or heat-stable enterotoxin, nor were isolates invasive on Sereny testing or tissue-culture assays. The organism, however, did produce a nonbloody diarrhea in infant rabbits. The laboratories of the U.S. Department of Agriculture and Pennsylvania State University reported no *E. coli* 0157:H7 from animals in the United States. The CDC laboratory detected only one strain of *E. coli* 0157:H7 among over 3000 *E. coli* organisms serotyped since 1973; it was isolated from a 50-year-old California woman in 1975 during an acute, self-limited afebrile illness with severe abdominal cramps followed by grossly bloody diarrhea.

## DISCUSSION

Two outbreaks of a clinically distinctive diarrheal illness occurred three months apart in two widely separated areas of the country among persons who had eaten at restaurants of a single fast-food chain. A rare *E. coli* serotype, 0157:H7, was isolated from ill patients in both outbreaks and from a retained specimen of hamburger patty from a suspected lot in the Michigan outbreak. We hypothesize that on two occasions, *E. coli* 0157:H7 contaminated the meat before it was made into hamburger patties, survived the cooking procedures at the restaurants, and caused illness

among some people who ate the meat. Apparently, failure to use meat by lots permitted cases to occur during a prolonged period in both outbreaks. The low attack rate in both outbreaks suggested a low level of contamination of a large volume of raw meat, reduction of the inoculum by cooking, or unknown host susceptibility factors. The pathogenesis of the illness and the source of contamination of the raw meat by this *E. coli* serotype are not known.

The evidence that *E. coli* 0157:H7 was the etiologic agent in these outbreaks may be summarized as follows. In two outbreaks this serotype was isolated from ill persons but not from healthy persons, ill persons with other forms of diarrhea, or patients who had completely recovered from bloody diarrhea. The only other isolate of *E. coli* 0157:H7 identified at the CDC was from a patient who had an identical disease in 1975. Preliminary studies indicate that this *E. coli* produces nonbloody diarrhea in infant rabbits, whereas *E. coli* isolates from two human control stool specimens do not (Potter ME: personal communication).

The clinical presentation of this illness may be distinguished from that of the bloody diarrhea or dysentery described in shigellosis, amebiasis, campylobacteriosis, or invasive *E. coli* gastroenteritis by the lack of fever and the bloody discharge resembling lower gastrointestinal bleeding. However, like other causes of bloody diarrhea, *E. coli* 0157:H7 may produce a spectrum of illness. In Michigan there was evidence of nonbloody diarrhea among persons who ate the same foods implicated at restaurants of Chain A. Our case definition, which required the presence of bloody diarrhea, would have excluded milder cases of this illness.

The case report of bloody diarrhea associated with *E. coli* 0157:H7 in 1975 suggests that this disease has occurred sporadically in the past. Descriptions of sporadic cases of a similar illness, frequently associated with antimicrobial use and distinct from pseudomembranous colitis, have been reported from several countries, including Japan and the United States.<sup>1-5</sup> Sakurai et al. reported that colonoscopy revealed areas of diffuse mucosal hemorrhage or erosion, mostly in the right colon; biopsy specimens of the mucosa showed little or no inflammatory change.<sup>1</sup> In the Oregon and Michigan outbreaks, only one patient in Oregon had been receiving an antibiotic (penicillin) before the onset of illness. Other reports have described cases of hemorrhagic colitis not associated with antimicrobial agents<sup>1</sup> or cases of so-called ischemic colitis in young adults.<sup>11</sup> Some of these may represent sporadic cases of the same illness that we have described in these outbreaks.

Acute hemorrhagic enterocolitis has been reported in patients with *K. oxytoca* isolated from their stools,<sup>12</sup> but no control stool cultures were obtained. In the two outbreaks that we investigated, strains of *K. oxytoca* were of several serotypes and were isolated from cases and controls. Although *B. pumilus* can induce enterocolitis in guinea pigs given clindamycin,<sup>13</sup> the *B. pumilus* isolates obtained in the two outbreaks were isolated

from both cases and controls and appeared to include more than one strain.

*E. coli* can cause diarrhea by direct invasion of the intestinal mucosa and by elaboration of heat-stable enterotoxins or of heat-labile resembling cholera toxin.<sup>14-16</sup> Our laboratory studies have shown that strain 0157:H7 does not cause disease by these mechanisms. Strains of *E. coli* that cause diarrhea by poorly defined mechanisms have been studied, but they do not typically cause bloody diarrhea.<sup>17-19</sup> *E. coli* 0157:H7 may cause diarrhea by an as yet unknown mechanism, perhaps by the production of previously unrecognized enterotoxins.

Isolation of *E. coli* 0157:H7, a rare serotype, from cases in two outbreaks of bloody diarrhea, from the suspected vehicle for the outbreaks, and from a sporadic case of bloody diarrhea in 1975 strongly suggests, but does not prove, that it caused the illness; proof may require studies using animal models and perhaps human volunteers. Similarly, the epidemiology, clinical spectrum, and pathogenesis of this unusual illness and the reservoir of the putative etiologic agent are still poorly understood or unknown and require continued clinical, epidemiologic, and laboratory studies.

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## MEDICAL PROGRESS

### ABDOMINAL SURGERY

#### (Second of Three Parts)

CLAUDE E. WELCH, M.D., AND RONALD A. MALT, M.D.

#### COLON

##### Colonoscopy

One of the important uses for colonoscopy is to detect the source of rectal bleeding when the results of a barium enema examination and a rigid sigmoidoscopy are normal. Among 306 patients at the Cleveland Clin-

ic who had rectal bleeding,<sup>112</sup> probable sources were found in 30 per cent, including polyps over 0.5 cm in diameter in 14 per cent and cancer in 8 per cent. One hundred five patients also had diverticulosis, which in the absence of colonoscopy would have been assumed to be the source of the bleeding. In 10 per cent of the cases the cecum could not be reached.

The short flexible colonoscope was designed to examine the left colon. Obviously, it will detect many lesions but miss others that could have been seen by total colonoscopy. In the Cleveland Clinic series 44 per

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